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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,522	11/28/2001	Roger Coleman	PF-0041-4 CON	5024

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/997,522	COLEMAN ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- Th MAILING DATE f this communication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9,10,12-16,28,29,46,47 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *1,14-16,28,29,46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7,9,10,12,13,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment C, filed 11/19/02, has been entered into the record.

B. The Declaration under 37 CFR 1.132, filed 11/19/02, has been entered into the record.

C. Claims 1, 3-7, 9, 10, 12-16, 28, 29, 46, 47 and 56-58 are pending in this application and claims 3-7, 9, 10, 12, 13 and 57-58 are the subject of this Office Action.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Objections

A. The objection to claim 5 has been withdrawn in view of Applicants' amendment to the claim to recite "The."

3. Claim Rejections - 35 USC § 101

A. Claims 3-7, 9, 10, 12, 13 and 57-58 remain rejected under 35 USC 101 for the reasons already of record on pages 3-5 of the Office Action dated 9/3/02. Applicants argue that the nucleic acid of the present invention encodes a human thrombin GPCR which has numerous uses in toxicology testing, drug development and the diagnosis of disease, none of which require knowledge of how the encoded polypeptide functions biologically. Applicants further argue that all GPCRs have utility and that there is no need for applicants to prove more than this substantial likelihood that the protein encoded for by the nucleic acid molecule of the invention in order to establish a utility. A Declaration under 37 CFR 1.132 by Lars Furness describes further uses of the polypeptide, including gene and protein expression monitoring (e.g. 2-D PAGE and Western blots) and that these techniques provide a specific benefit to the public and are well-estbalished. Applicants also argue that the protein of the present invention is homologous to, but significantly different from HUMTHRR and is also similar to PAF receptor.

These arguments have been considered, but are not deemed persuasive. First, Applicants have only shown that the protein of the present invention is homologous to HUMTHRR, but is significantly different. Furthermore, the protein of the present invention is also shown to be homologous to PAF, but only over certain regions. Therefore, the fact that the protein of the present invention is homologous to 2 different proteins further demonstrates that the function of this protein is not known.

Additionally, the use of the protein of the present invention in toxicology control screening is not deemed persuasive since, this is not a specific utility of the protein of the present invention. Any protein can be used in these screening assays. Therefore, there is no specific benefit that can be attributed to the protein of the present invention, or to its encoding nucleic acid. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptides. In order for a polypeptide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptides to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptides are either present only in diseased tissue to the exclusion of normal tissue or are expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polypeptides and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. It is the group of proteins *as a whole* which may have a utility in toxicology screening.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Furthermore, if the function of the protein of the present invention is not known, one cannot determine through toxicology testing that potential ligands would or would not be toxic, since an alteration of protein expression alone is not a definitive toxicological endpoint.

Regarding Applicants' arguments on the bottom of page 20 of the response dated 11/19/02, TRH would be useful if Applicants, in fact, did show that the protein of the present invention was, in fact, a TRH. The middle of page 21 states that the protein would be useful in the diagnosis and treatment of immune disorders and trauma. Respectfully, the terms "immune disorders" and "trauma" are vague and non-specific. Again, not knowing that the protein actually encodes a TRH would not allow the artisan to determine the protein's utility in any associated diseases. Applicants further state on the top of page 22 that proteins known to be DNA ligases have been considered by the Office to have utility. However, the

function of these proteins is known and the identification of the protein as a DNA ligase would not be based on homology. Applicants argue that histone proteins would not be a suitable target for drug development due to possible fatal effects. However, first, this assumes that the protein has been identified as a histone based on experiments other than homology. Second, it is clear what can happen to a patient with altered histone function since these protein have been thoroughly characterized. The function of the protein of the present invention is not clear since, unlike the exemplified histones, has not been characterized. Finally, the uses disclosed on the bottom of page 23 of the response are not specific to the protein of the present invention, as any, or at least a large number of proteins can be used for such purposes.

4. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 3-7, 9, 10, 12, 13 and 57-58 remain rejected under 35 USC 112, first paragraph for the reasons already of record on page 6 of the Office Action dated 9/3/02 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

B. Claims 3-7, 9, 10, 12, 13 and 57-58 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 6-8 of the Office Action dated 9/3/02. Applicants have amended the claims to recite that the "naturally occurring amino acid sequence" differs from SEQ ID NO:2 by the substitution, insertion, or deletion of 1-5 residues. However, it is not known if the total number of alterations is at most 5, or if 1-5 alterations can occur at each amino acid residue of SEQ ID NO:2. The insertion of a limitation that demonstrates that the naturally occurring protein has a function specific to that of the wild-type protein of SEQ ID NO:2 is also recommended, such as "wherein the variant binds thrombin."

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may

also be critical determinants of antigenicity. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Regarding the recitation of "thrombin-binding fragment," Applicants argue that the specification discloses methods of measuring the binding of a fragment of SEQ ID NO:2 to any agent which can affect signal transduction. However, regarding *Marzocchi*, the Office believes that that the guidance provided by the specification would not be sufficient to enable the artisan to make the claimed fragment of SEQ ID NO:2 which binds thrombin. The protein of SEQ ID NO:2 is 381 residues in length and Applicants have not provided the artisan with any information (i.e. guidance or working examples) as to which residues are required to bind thrombin, nor is it predictable to the artisan which residues would need to remain as part of the fragment in order to retain the thrombin-binding property of the fragment.

Regarding the claims reading on naturally occurring allelic variants of SEQ ID NO:2, Applicants argue that, through the process of natural selection, nature would have determined the appropriate amino acid sequences and that, given the amino acid sequence of SEQ ID NO:2, the artisan would have been able to obtain "naturally occurring allelic variants" using, for example, hybridization techniques to screen a cDNA library. As stated on page 7 of the Office Action dated 9/3/02, the Examiner cannot determine how one would distinguish, merely by examination of the protein, whether a protein were the result of expression of a different allele, or alternatively, were merely one of a number of ultimate species that might be obtained by the expression of SEQ ID NO:1 disclosed in this application. Enablement is not commensurate in scope with claims to proteins potentially encoded for by allelic variants of SEQ ID NO:1, or those of SEQ ID NO:2. Allelic variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants, nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function.

Regarding "at least 60 contiguous nucleotides" of SEQ ID NO:2, Applicants have not specifically addressed this issue. Regardless, this rejection is maintained for the reasons already of record as well as

for the reasons stated in this rejection. Since the utility of the nucleic acid molecule encoding SEQ ID NO:2 is not known, then the utility of any polynucleotide fragment thereof would also not possess utility.

Due to the large quantity of experimentation necessary to obtain "naturally-occurring" variants, to generate the potentially large number of derivatives recited in the claims, and to determine the specific activity of these variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 3, 6, 7, 9, 12, 13, and 58 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 8 of the Office Action dated 9/3/02. Applicants argue that they have amended the claims to recite that the "naturally occurring amino acid sequence" differs from SEQ ID NO:2 by the substitution, insertion, or deletion of 1-5 residues. However, it is not known if the total number of alterations is at most 5, or if 1-5 alterations can occur at each amino acid residue of SEQ ID NO:2. The insertion of a limitation that demonstrates that the naturally occurring protein has a function specific to that of the wild-type protein of SEQ ID NO:2, such as "wherein the variant binds thrombin" would not overcome this rejection since Applicants have not adequately described which residues are required for the thrombin-binding capabilities of anything other than the full-length receptor of SEQ ID NO:2. As stands, the specification has only described the full-length protein of SEQ ID NO:2.

Applicants also argue that polypeptide fragments, including "thrombin-binding fragments" are described on pages 5, 6, 12 and 21 of the specification and methods of measuring this binding ability are also described. Applicants further argue that, given SEQ ID NO:2, the artisan would recognize polynucleotides encoding fragments of SEQ ID NO:2 and would be able routinely determine whether any fragment of SEQ ID NO:2 possessed thrombin-binding activity. First, these pages of the specification only define the term "fragment" and briefly discuss "immunogenic fragments" of SEQ ID NO:2. They do not provide any description of the sequence of any "thrombin-binding fragments." Again, though the artisan would be able to identify a fragment of SEQ ID NO:2, the artisan would not be able to routinely identify thrombin-binding fragments of SEQ ID NO:2. Applicants have not described which residues are critical to maintain the thrombin-binding characteristics of the claimed fragment. Therefore, one of ordinary skill in the art would not be able to routinely identify these fragments of SEQ ID NO:2 which

retain thrombin-binding activity in the absence of adequate description as to what amino acids constitute this fragment.

B. Claims 3, 6, 7, 9, 12, 13, and 58 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 9-10 of the Office Action dated 9/3/02. Applicants argue that they have amended the claims to recite that the "naturally occurring amino acid sequence" differs from SEQ ID NO:2 by the substitution, insertion, or deletion of 1-5 residues and that SEQ ID NO:1 and 2 are disclosed in the specification. Applicants further argue that the degeneracy of the genetic code would provide for a number of TRH-encoding nucleotide sequences, some bearing minimal homology to any known naturally occurring gene may be produced. Applicants also argue that given any naturally occurring polypeptide sequence, one of ordinary skill in the art would routinely be able to recognize whether it was a variant of SEQ ID NO:2.

On pages 35-37 of Applicants response, they argue that the subject matter of the claims is different from that of Lilly and Fiers since the subject matter of the present claims is defined in terms of a chemical structure of SEQ ID NO:1 and 2 and that there is no reliance in the present case merely on a description of functional characteristics of the polynucleotides and polypeptides and that the polynucleotides of the present invention recite structural features. These arguments have been considered, but are not deemed persuasive. While the feature of "variant of SEQ ID NO:2" may be arguable as being a functional characteristic of SEQ ID NO:2, the claims still read on allelic variants and Applicants have not demonstrated that they were in possession of allelic variants of SEQ ID NO:1 or 2 at the time of the present invention. The concept of a naturally occurring allelic variant of SEQ ID NO:1 or 2 was, respectfully, merely an idea. Lilly stated that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Again, at section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention." This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. It is not clear that Applicants were in possession of any allelic variants of SEQ ID N:O1 or 2. Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1 and 2 and equivalent degenerative codon sequences thereof, as well as SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

6. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claims 3, 6, 7 and 9 under 35 USC 112, second paragraph, regarding "thrombin-binding fragment" has been withdrawn in view of Applicants' amendments to the claims.

7. Statutory Double Patenting

A. Claims 4, 5 and 57 remain rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 3 of prior U.S. Patent No. 5,686,597. The only difference in the literal claims is the adjective "isolated" vs. "purified." The specification does not define these terms.Both of these claims still evidence the hand of man. Purified is a relative term, and only means 'removed from its natural source', unless otherwise defined in the specification. It specifically does NOT mean homogeneous. Therefore, unless otherwise defined, 'isolated' means the same as 'purified', and 'isolated and purified' is merely redundant.

8. Obviousness-Type Double Patenting

A. Claims 3, 4, 5, 12, 13 and 57 remain rejected under the obviousness-type double patenting rejection on pages 12-13 of the Office Action dated 9/3/02 as being obvious over claim 1 of patent 5,869,633. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

B. Claims 3, 4, 5, 12, 13 and 57 remain rejected under the obviousness-type double patenting rejection on pages 13-14 of the Office Action dated 9/3/02 as being obvious over claims 1 and 3 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

C. Claim 6 remains rejected under the obviousness-type double patenting rejection on pages 14-15 of the Office Action dated 9/3/02 as being obvious over claim 2 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

D. Claims 9 and 10 remain rejected under the obviousness-type double patenting rejection on pages 15-16 of the Office Action dated 9/3/02 as being obvious over claim 6 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

E. Claims 6 and 7 remain rejected under the obviousness-type double patenting rejection on page 16 of the Office Action dated 9/3/02 as being obvious over claims 4 and 5 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

9. Conclusion

A. No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 10, 2003

Gary L. Kunz
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